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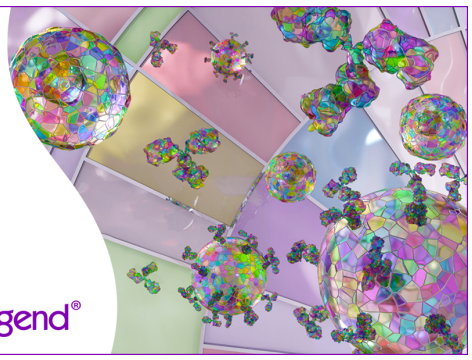

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Brief Reviews

The Journal of Immunology

Immune Dysfunction and Bacterial Coinfections following Influenza

Dennis W. Metzger and Keer Sun

Secondary pulmonary infections by encapsulated bacteria including *Streptococcus pneumoniae* and *Staphylococcus aureus* following influenza represent a common and challenging clinical problem. The reasons for this polymicrobial synergy are still not completely understood, hampering development of effective prophylactic and therapeutic interventions. Although it has been commonly thought that viral-induced epithelial cell damage allows bacterial invasiveness, recent studies by several groups have now implicated dysfunctional innate immune defenses following influenza as the primary culprit for enhanced susceptibility to secondary bacterial infections. Understanding the immunological imbalances that are responsible for virus/bacteria synergy will ultimately allow the design of effective, broad-spectrum therapeutic approaches for prevention of enhanced susceptibility to these pathogens. ***The Journal of Immunology*****, 2013, 191: 2047–2052.**

Respiratory viruses such as influenza virus are known to cause severe disease and to be associated with pneumonia, particularly in the very young and aged populations, and in individuals with serious medical comorbidities. Additionally, respiratory virus infection can often lead to increased susceptibility to secondary bacterial infections. The mechanisms responsible for this viral/bacterial synergy have remained elusive and historically have been attributed to virus-induced lung tissue damage (1, 2). However, by exploiting recently developed animal models, a dysfunctional host antibacterial immune response during influenza infection has been implicated as the major contributor to secondary bacterial susceptibility (3). In this paper we review recent scientific progress that has shed new insight into this major clinical problem.

The clinical scenario and relevant animal models

It is well known that bacterial pneumonia often occurs following influenza infection. These secondary infections predominantly involve a selected group of bacteria, including *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pyogenes*. Such coinfections may be particularly problematic during influenza pandemics. Indeed, reviews of published autopsy case reports revealed that >90% of deaths during the 1918 influenza pandemic likely resulted from secondary pneumococcal pneumonia (4, 5). One could argue that antibiotics were not available in 1918 and thus secondary bacterial infections would likely not represent a serious problem today. Nevertheless, most deaths in the 1957–58 "Asian influenza" pandemic were still due to secondary bacterial pneumonia, even with the availability of antibiotics (6). In one study, 75% of confirmed fatal cases of influenza in the 1957–58 pandemic had bacteriological and histological evidence of bacterial pneumonia, mainly due to *S. aureus* or *S. pneumoniae* (7). The remaining fatal cases appeared to be caused primarily by influenza viral pneumonia. Furthermore, in the more recent 2009 H1N1 (swine flu) pandemic, >50% of the people who died showed histologic and microbiologic evidence of bacterial pneumonia (8). Strikingly, one report noted that 43% of the children who died of the H1N1 virus in the United States from April to August 2009 had laboratory-confirmed bacterial coinfections, including all six children that had culture or pathology results reported and no recognized, high-risk medical conditions (9). In another report, it was found that among 317 pediatric deaths associated with the H1N1 virus from April 2009 to January 2010, 28% had evidence of bacterial coinfection, predominantly *S. aureus* and *S. pneumoniae* (10). It should be recognized that, given the difficulty and uncertainty of detecting and cultivating bacteria from the lungs of deceased patients, the numbers of coinfected patients in all of these studies could be significantly higher.

Coinfections are also a continuing problem with seasonal influenza. Approximately 90,000 people die of bacterial infections in the United States each year, and during the past 20 y, methicillin-resistant *S. aureus* (MRSA) has emerged as a growing problem for both hospital- and community-acquired pneumonia. Indeed, more people die of MRSA than from HIV (11, 12). Additionally, new variants of MRSA continue to emerge as pulmonary pathogens and have been associated with both community outbreaks and postinfluenza pneumonia (13, 14). It has been estimated that bacterial coinfections are found in 4–30% of adults and in 22–33% of children that are hospitalized with community-acquired viral pneumonia (15). Again, most of these infections are due to *S. aureus* or *S. pneumoniae*.

The mouse infection model is well accepted for studying influenza infection. In both humans and mice, influenza virus titers in the lung reach a peak at 3–5 d after infection, and the

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Abbreviation used in this article: MRSA, methicillin-resistant *S. aureus*.

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virus begins to be cleared thereafter, with resolution of infection nearly completed by days 10–12. Murine models of viral/bacterial coinfection have also been established by several groups (16–20), and these models appear to accurately mimic clinical observations regarding the high susceptibility to secondary bacterial infection following influenza, with greatly enhanced disease severity and fatality rates. The viral strain most commonly used for murine coinfection studies is the mouse-adapted H1N1 A/PR/8/34, but nonadapted H1N1 CAL/04/09 has also been employed (21). The greatest susceptibility to secondary bacterial infection in both humans and mice is seen around day 7, at the time of influenza virus clearance, and lasts approximately 1 wk (Fig. 1). Nonetheless, there are differences in the detailed experimental conditions used in different mouse studies, and these differences are mainly related to whether the individual focus is on understanding influenza-induced susceptibility to secondary bacterial infection or the resulting poor disease outcome. For example, many studies (22–24) have used very high bacterial challenge doses, particularly when studying influenza and *S. aureus* coinfection, which leads to extensive neutrophil recruitment and exacerbation of inflammation, a clinical feature that ultimately can result in bacterial pneumonia and a poor outcome. Similarly, some studies (25, 26) have focused on the late stages of bacterial infection (24 h or later after secondary infection), again when there is an influx of neutrophils into the lung and intense inflammatory responses due to bacterial outgrowth. Thus, investigators using high doses of challenge bacteria and/or investigating the latter stages of infection typically end up studying neutrophil function, either their antibacterial activities or accompanying inflammatory lung damage. Alternatively, our experiments have indicated that a normal mouse can effectively clear up to $\sim 10^5$ pneumococci very early (within 4–12 h); higher challenge doses require recruitment of neutrophils for survival (3). We have used this system to examine phagocytic function very early after bacterial infection, thus avoiding the confounding issue of whether the observed pathology is due to failure to control the initial bacterial infection versus the overwhelming inflammatory response following the infection. We suggest that using the smallest viral and bacterial doses necessary to observe pathogen synergy, a situation that most closely mimics the natural clinical scenario, is optimal for studying the mechanism of influenza-induced susceptibility to secondary bacterial infection.

Virus-mediated lung damage

The mechanisms responsible for synergy between influenza virus and bacterial infections have remained puzzling since 1918. It is clear that increased susceptibility to various encapsulated bacteria occurs following influenza infection (27), suggesting a general defect. Influenza virus replicates preferably in epithelial cells, which leads to direct damage to the airway epithelium. Historically, the generally accepted mechanism responsible for microbial synergy is that this virus-induced damage to the epithelial barrier provides increased attachment sites for bacteria, resulting in invasive disease (1, 2). Influenza-induced lung tissue damage in both humans and mice is greatest on day 6 after infection (28), which generally correlates with the time of greatest susceptibility to bacteria. However, viral strains that cause minimal epithelial cell damage still enhance subsequent bacterial infection in mice (29, 30). Influenza neuraminidase and upregulation of platelet-activating factor receptor expression during murine viral infection may increase bacterial adherence (31, 32), although use of mice deficient in platelet-activating factor receptor or treatment of mice with a competitive receptor antagonist had no influence on survival rates after bacterial infection (19, 33). Furthermore, genetic deletions that modify viral neuraminidase expression do not affect susceptibility of mice to secondary bacterial pneumonia (34). Finally, there was no correlation between human mortality and virus attack rates in 1918 (35), suggesting factors other than simply viral-induced lung damage.

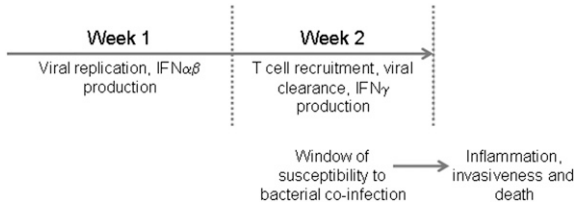

FIGURE 1. Kinetics of influenza virus infection and susceptibility to bacterial coinfection.

Influenza-induced suppression of antibacterial innate immunity

A concept that has recently gained traction in the field is that innate bacterial clearance in the lung is somehow impaired by influenza infection. Alveolar macrophages are the major cell population in the normal airway, and these cells form the first line of defense against respiratory infection. A deficiency in alveolar macrophage–mediated phagocytosis following influenza has been reported (36–38). However, in most of the reported studies, inhibition of phagocytosis was only partial. For example, in the study by Warshauer et al. (38), 90% of *Staphylococcus epidermidis* was killed by alveolar macrophages obtained from uninfected mice versus only 68–73% killing by macrophages from influenza-infected animals. Jakab et al. (39, 40) reported defective phagolysosome formation by alveolar macrophages from virus-infected mice but no defect in phagocytosis, whereas Nugent and Pesanti (41) found no defect in either uptake or killing. The discrepancies in results from these various laboratories could be due to several factors, including differences in the days elapsed since initial virus infection and/or secondary bacterial challenge, differences in doses of virus and bacteria used, and variations in the combinations of virus and bacterial strains studied.

More recently, it has been found that alveolar macrophage–mediated clearance of *S. pneumoniae* that occurs within 4–6 h following intranasal bacterial challenge is, in fact, significantly inhibited by prior influenza virus infection, with maximal inhibition occurring on days 7–8 following viral infection (3). Interestingly, this is when effector T cells have migrated into the lung airways to initiate recovery from viral infection (42) and is the time of peak IFN-γ expression in the pulmonary tract. Indeed, whereas bacterial clearance is suppressed in wild-type mice after influenza infection, this suppression is nearly absent in virus-infected IFN-$\gamma^{-/-}$ mice and in wild-type mice treated with neutralizing anti–IFN-γ mAb after influenza infection (3). Furthermore, treatment of non-virus–infected mice with exogenous IFN-γ can mimic viral infection and result in inhibition of alveolar macrophage–mediated bacterial phagocytosis (3). A critical role for IFN-γ in inhibiting phagocytosis of *S. aureus* by alveolar macrophages has similarly been reported

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(43). Further experiments showed that the relatively high levels of IFN-γ in the lung following influenza caused inhibition of MARCO expression (3), the scavenger receptor necessary for recognition of nonopsonized pneumococci by alveolar macrophages (44). Thus, although low doses of IFN-γ are traditionally known to enhance intracellular killing of bacteria, high levels of IFN-γ in the lung downregulate expression of the scavenger receptors required for bacterial recognition by lung macrophages, such as MARCO (3) and the mannose receptor (45), and thus inhibit binding and uptake by these cells. It has been suggested that impaired NK cell activity during secondary *S. aureus* infection leads to inhibition of alveolar macrophage phagocytosis and enhanced susceptibility to invasive bacterial disease, possibly due to decreased TNF-α expression (46), but this potential mechanism has yet to be fully examined.

Note that in normal mice infected only with pneumococci, increased expression of IFN-γ can enhance TNF-α expression and thereby lead to increased neutrophil recruitment (47). However, in animals previously infected with influenza virus, TNF-α production is decreased even in the presence of IFN-γ (3, 48). This is probably related to the finding that influenza infection leads to desensitization of TLR4-mediated signaling (48). However, although pneumolysin made by pneumococci is a ligand for TLR4, there is no evidence that immunity to *S. aureus* depends on TLR4. Furthermore, this TLR signaling defect is relatively long-lasting and still observed several months after viral infection. Thus, a potential effect on TLR signaling does not track with clinical susceptibility to secondary bacterial infection, which normally occurs within a 1-wk window following influenza virus infection. Nevertheless, this effect may be related to defects in restoration of lung homeostasis (see below).

In agreement with earlier human studies (49–51), McNamee and Harmsen (23) reported significant neutrophil dysfunction in the lungs of influenza virus and pneumococcus doubly infected mice. However, neutrophil impairment was observed on both days 3 and 6 after influenza infection whereas enhanced susceptibility to *S. pneumoniae* infection was seen only on day 6. Expression of inhibitory IL-10 that is induced by 2,3-dioxygenase in influenza virus–infected hosts has been reported to be partially responsible for the increased susceptibility to secondary bacterial infection, likely due to an effect on neutrophil function (22, 25). However, only a minimal decrease in susceptibility to secondary bacterial infection is observed in IL-$10^{-/-}$ mice (3, 25). Furthermore, IL-$10^{-/-}$ mice clear influenza infection more quickly than do wild-type animals due to earlier induction of adaptive immunity (52, 53). This, in turn, alters the window of enhanced susceptibility to bacterial infection, an effect that may account for the earlier findings.

Shahangian et al. (54) found that mice deficient for the IFN-α/β receptor were partially resistant to secondary infection with *S. pneumoniae* following influenza, and this effect correlated with production of neutrophil chemoattractants. A similar function for IFN-α and IFN-β was reported in a mouse model of upper respiratory tract pneumococcal colonization (55). An important role for the Th17 pathway in this effect was shown by the finding that IL-17, IL-22, and IL-23 were decreased following coinfection with influenza virus and *S. aureus*, and that this decrease was dependent on type 1 IFN (56). Furthermore, intentional overexpression of IL-23 during influenza led to markedly improved bacterial clearance. Similarly, Ivanov et al. (57) recently reported that IL-22–deficient mice were significantly more susceptible to pneumococcal infection following influenza. It has been found in other infection models that IL-17–producing γδ T cells can be particularly suppressed by type 1 IFN (58), and indeed this has been reported to occur during secondary pneumococcal infections following influenza (59). In summary, it appears that in addition to decreased alveolar macrophage function following lung viral infection, it is likely that induced type 1 IFN production can also inhibit IL-17–mediated neutrophil recruitment, possibly by targeting γδ T cells (Fig. 2).

Defects in restoration of lung homeostasis

As summarized above, multiple studies have demonstrated that impaired antibacterial immunity predominantly contributes to lethal influenza and bacterial coinfection, and inhibited innate antibacterial immunity is associated with dysregulated pulmonary cytokine responses following influenza infection. Alternatively, these immune regulators, such as type I IFN (60), IL-10 (52), and IL-17 (61, 62), often have opposite influences on protective antiviral immune responses. Failure to maintain either appropriate antiviral or antibacterial immune responses can have detrimental effects on the outcome of coinfection. This may help explain the greatly enhanced disease severity and fatality rates associated with influenza and bacterial coinfection.

In addition to enhanced bacterial outgrowth, virus-induced lung damage and loss of associated repair responses may also contribute to a lethal outcome following secondary bacterial infection (63). Moreover, it is known that at the recovery stage of influenza infection, multiple anti-inflammatory immune responses are upregulated to restore airway epithelial integrity and lung homeostasis, including CD200/CD200R interactions (64, 65), innate lymphoid cell function (66), T cell–mediated IL-10 production (67), and PGE_2 expression (68). Although there is still a lack of direct evidence that these immune regulators inhibit macrophage or neutrophil antibacterial activities following influenza infection (69, 70), it was found that influenza infection leads to desensitization of alveolar macrophage TLR signaling and susceptibility to secondary bacterial infection even long after viral clearance (48).

Recent coinfection studies have mostly focused on the mechanism responsible for influenza-induced susceptibility to secondary bacterial infection. However, note that broad pulmonary inflammatory infiltration is a key clinical feature of bacterial pneumonia. Overwhelming bacterial infection may explain widespread lung pathology at later phases of infection. However, excessive inflammation was found to be independent of pulmonary bacterial burden (20). Additionally, immunopathogenesis of influenza and pneumococcal coinfection can be directly mediated by viral virulent factors such as PB1-F2 (71). Nonetheless, excessive inflammatory responses after establishment of secondary bacterial infection comprise another difficulty for the clinical management of disease (72, 73) and is likely the reason for enhanced disease severity and mortality despite appropriate antibiotic treatment.

Conclusions

Based on the various findings discussed above, it appears that an elicited adaptive immune response against viral infection (an intracellular pathogen) impairs innate immune defenses against bacterial infection (an extracellular pathogen). This would explain why secondary bacterial infections in the clinic occur at

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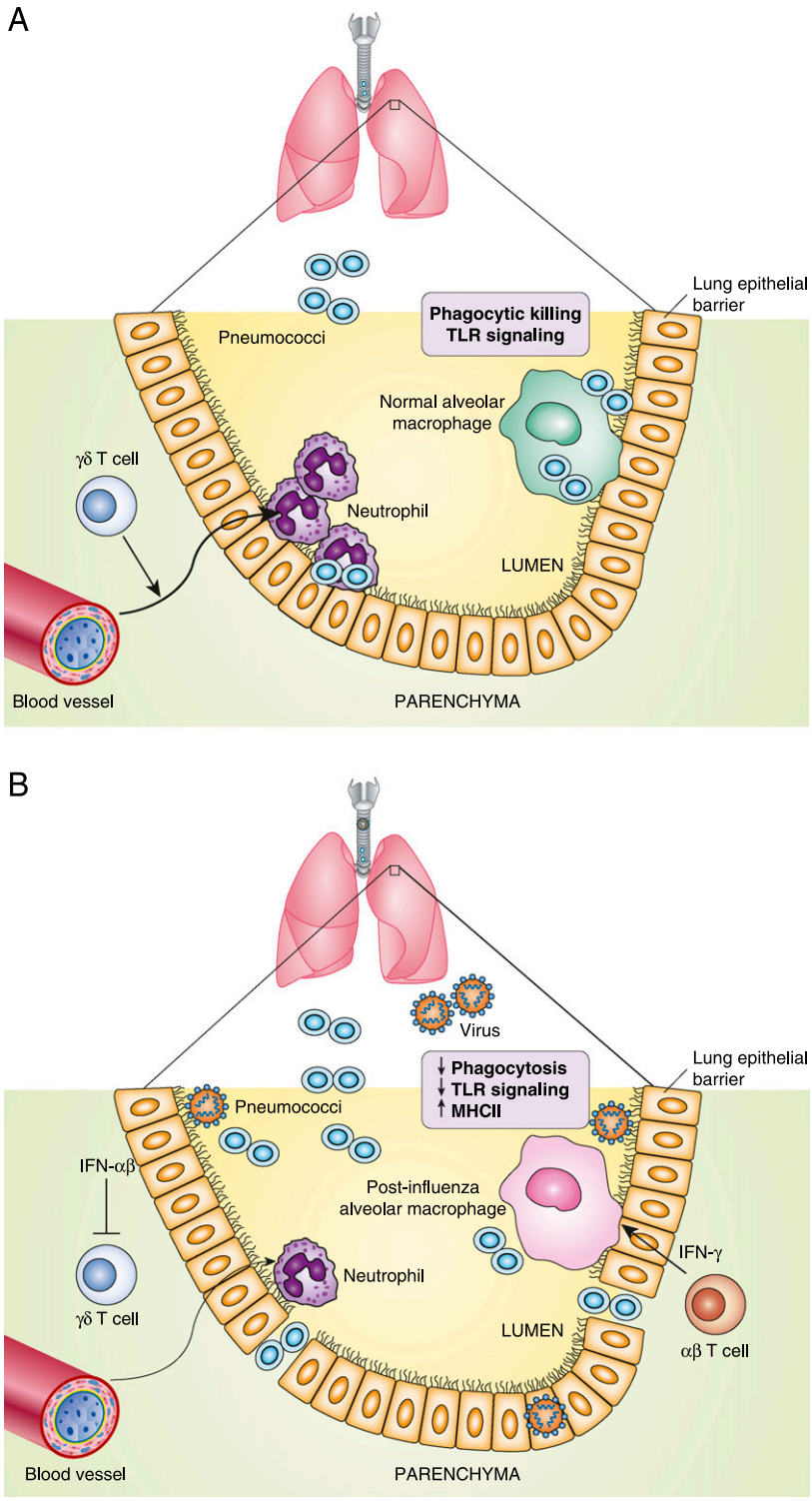

FIGURE 2. Model for the influence of influenza infection on innate antibacterial immunity. (**A**) In the normal, uninfected lung, resident alveolar macrophages provide the first line of defense against encapsulated bacteria such as pneumococci. When macrophage defenses are overwhelmed, neutrophils are recruited to the airways through the action of IL-17 and related cytokines, likely produced by γδ T cells. (**B**) During influenza infection, CD4 and CD8 T cells are recruited into the lung to help resolve viral infection. These T cells secrete copious amounts of IFN-γ, which binds to alveolar macrophages and modifies their properties, including inhibition of scavenger receptor expression, such as MARCO, and upregulation of MHC class II. Additionally, IFN-α/β produced by virally infected epithelial cells inhibits IL-17 production, and thus neutrophil recruitment is diminished. Not shown is the infiltration of other inflammatory myeloid cells into the lung following influenza. The result is that although adaptive immunity designed to establish antiviral immune memory is enhanced, innate antibacterial defenses are suppressed. By approximately day 14 following influenza infection, levels of type I and type II IFN are decreased and innate defenses against bacterial invasion are restored.

a time when the virus begins to be cleared from the lung and the patient enters the recovery stage. Although some investigators find a large decrease in total numbers of alveolar macrophages in influenza-infected lungs (74), other studies have not observed a significant reduction in numbers but rather have found a modified phenotype (3, 60, 75). This is accompanied by a change in function of the phagocytic lung cell population from cells that mediate basal levels of innate protection through phagocytosis and production of proinflammatory cytokines, to cells better attuned to Ag presentation and induction of adaptive immune responses. In fact, whereas alveolar macrophage expression of the scavenger receptor MARCO is downregulated by virus-induced IFN-γ, MHC class II expression is increased (3). Considering the fact that murine alveolar macrophages normally inhibit adaptive immune responses (76, 77), their modification on day 7 of influenza infection, together with type 1 IFN–mediated inhibition of neutrophil recruitment (Fig. 2), may be a mechanism that evolved to allow enhanced induction of specific anti-influenza T cell memory in the respiratory tract, albeit at the temporary expense of innate protection against bacterial pathogens. This new paradigm should ultimately allow development of novel immune intervention strategies for

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the broad-spectrum prevention and management of secondary bacterial infections following influenza.

Disclosures

The authors have no financial conflicts of interest.

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